

phocytosis; an absence of megaloblasts, and usually normoblasts. Postmortem: the characteristic finding is a pale bone-marrow in which the signs of erythrocytic and granulated leukocytic formation are wanting.

3. The differences between aplastic anemia and the usual form of progressive pernicious anemia result entirely from the absence of regenerative processes in the former.

4. The blood picture in aplastic anemia is the result of two factors, one the hemocytolysis, and the other the failure of regeneration on the part of the bone-marrow.

5. The failure of regeneration of the blood elements of the bone-marrow represents the result of one of the three following conditions: (a) A simple deficiency of the regenerative powers; (b) an inhibitive action on the bone-marrow by the factors producing the destruction of the blood elements; and (c) a true aplasia of the bone-marrow. If there be a true aplasia it is probably of recent origin, for if it were of long duration there would in all probability have been manifestations of a deficiency in blood formation before the advent of the hemolytic agent.

6. The relations of lymphocytes to leukocytes and red blood corpuscles in aplastic anemia lend evidence to the view that lymphocytes are not a specific product of the bone-marrow.

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## STUDIES IN THE NATURAL AND ARTIFICIAL INHIBITION OF PEPTIC DIGESTION.

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No matter how important the secretion of hydrochloric acid may be for the purpose of preparing the food for the action of pepsin, and for stimulating the production of pepsin and the secretion of the pancreatic, and probably of the intestinal juices, there can be no question, we think, that the actual work in the stomach of preparing the proteids for assimilation depends upon the peptic activity. Therefore it is exceedingly important in all cases of gastric disease to determine whether the peptic activity is normal or not, and whether, if it is normal under favorable experimental conditions, there may not be present in the gastric contents inhibitory factors which prevent, or make imperfect, the peptonization of the food.

A number of methods have been suggested for estimating the

peptic activity. Of these the only ones of value clinically are those of Hammerschlag and Mett. Both are good, and give results that are useful in diagnosis and for the purpose of controlling treatment. We have elsewhere stated our reasons for preferring the method of Mett. Our technique in the use of this method has already been described. It yields results that are practically the same as those of other investigators.

The object of the present investigation was to determine, first, the natural inhibitory factors in the gastric contents; second, the inhibitory action of certain substances, chiefly those used as food preservatives.

The natural factors may be substances secreted by the stomach itself, or products, either normal or abnormal, of the digestive activity. Danielewsky claims to have discovered a substance, anti-pepsin, which exists in the gastric mucosa. It inhibits the action of pepsin but does not destroy it; it may be extracted with weak acid solution; it is not destroyed by heating to 70° C. or even by brief exposure to 100° C. Hensel found that it is not precipitated by phosphotungstic acid. It is organic in nature, but not an albumin. A similar substance is obtained from various organs. Weinland and Schwartz have also studied this subject. The latter, by boiling a solution of pepsin, was able to demonstrate that it acquired inhibitory properties as a result of destruction of the pepsin and immunity of the anti-pepsin.

Nearly every type of food, the carbohydrates, the hydrocarbons, the proteids, and the products of their digestion, and the various mineral constituents, have been accused of inhibitory activity.

The method has undergone some trifling modifications in the course of the work. At first we used rather strong solutions of pepsin. In a quantity of 16 c.c., 5 c.c. consisted of 2 per cent. pepsin, and the remaining 11 c.c. of a dilution of the substance under examination, or, for the purpose of control,  $\frac{n}{20}$  HCl. The pepsin was dissolved in  $\frac{n}{20}$  HCl and the substance to be tested in the same solution, excepting in the case of liquid substances bulky enough to make it necessary to acidulate them to the same degree with concentrated HCl. The degree of inhibition that exists in strong pepsin solutions, however, is so great that we found the results were more uniform if weaker solutions were employed, and all our later experiments have been made with 1 c.c. of a 1 per cent. solution of pepsin and 15 c.c. of the test substance.

The preparation of the tubes, however simple, is of some importance. The best results are obtained with fairly thick-walled glass tubes of an internal diameter of between 1 and 2 mm. These are filled with albumin, boiled for five minutes, and, while boiling, rolled continually. The ends are then closed with sealing wax. The variations in the reading of these tubes are so slight as to be of no importance.

Our results, of course, exhibit only one phase of the subject, and that is the effect of the test substances upon peptic digestion under apparently favorable conditions for its manifestation. In the stomach a number of factors are at work altering the composition of the gastric contents. These are: The ingestion of food, water, or saliva; the secretion of gastric juice; the secretion of mucus; osmosis; the discharge of the stomach contents through the pylorus; and, occasionally, the regurgitation of the duodenal contents into the stomach. In the case of saline solutions osmosis becomes a very important factor, and probably if strong they are rapidly diluted.

The technical difficulties of studying the effect of various substances upon the peptic activity within the stomach are very great; nevertheless, we have attempted to overcome them in a series of experiments which is still fragmentary and incomplete. It must not be forgotten, moreover, that in all these experiments the peptic activity varies not in accordance with a simple numerical proportion, but in proportion to the square root of the degree of concentration of the pepsin. This law was first determined by Schuetz, working with an exceedingly cumbersome method, and afterward restated by Borissow. Samojloff found that it did not hold good for strong solutions, either in artificial pepsin solutions or the actual gastric juice. In the course of our work we have noted some very good illustrations of this law.

TABLE I.

|                |     |        |
|----------------|-----|--------|
| Pure           | 2.2 | (4.84) |
| $\frac{1}{2}$  | 2.4 | (5.76) |
| $\frac{1}{4}$  | 2.2 | 4.84   |
| $\frac{1}{8}$  | 1.4 | (1.96) |
| $\frac{1}{16}$ | 1.1 | 1.21   |
| $\frac{1}{32}$ | 0.8 | 0.64   |
| $\frac{1}{64}$ | 0.5 | 0.25   |

TABLE II.

|                |     |       |
|----------------|-----|-------|
| Pure           | 4.9 | 24.01 |
| $\frac{1}{4}$  | 4   | 16    |
| $\frac{1}{8}$  | 2.7 | 7.29  |
| $\frac{1}{16}$ | 1.9 | 3.61  |

In both tables it will also be observed that in the pure gastric contents inhibition was present. We shall discuss this more fully in a subsequent paragraph.

Schuetz's law is exceedingly interesting. Why pepsin should show the peculiar quality of diminishing in activity according to the square root of the degree of dilution—a quality, so far as we know, possessed only by it and a few other ferments—has never been clearly elucidated. An hypothesis that has occurred to us would serve in a measure to explain it, although, aside from the fact of being a satisfactory explanation, there is no other proof of its correctness. This is, that the peptic ferment consists of discrete particles. Either these particles are in continual activity and mutually interfere with one another in their movements, or else they radiate activity and the emanations from different particles interfere. To our minds the former hypothesis seems by far the more satisfactory, but in either case increase in the distance between the

individual particles would cause an increase in their capacity for activity proportionate to the square of the distance, and inversely as the degree of concentration. Conversely, the effect of concentration would be to increase the peptic activity not directly, but in proportion to the square root of the degree of concentration. This accords with the results obtained by experiment. In high concentrations the inhibition is greater than the law would indicate, as is clearly shown in the following experiment:

|                    |                                 |                                |     |
|--------------------|---------------------------------|--------------------------------|-----|
| Pepsin 1 per cent. | 6.7                             | Pepsin $\frac{1}{4}$ per cent. | 4.3 |
|                    | Pepsin $\frac{1}{16}$ per cent. | 2.5                            |     |

If, in the gastric contents, the inhibition were of moderate degree the diminution of peptic activity in concentrated solutions would be sufficient explanation for it. Investigation, however, has shown that the inhibition is actually much greater than can possibly be explained by any concentration of the solution, being sometimes absolute, when pure gastric contents is tested, although in lower dilutions peptic activity is fairly strong. The following table of a series of cases taken in the order of their testing illustrates this fact very clearly. It has been arranged as follows: In the first column, the case number; in the second, the total acidity of the gastric contents under investigation; in the third, the peptic activity of the pure gastric contents; in the fourth, the peptic activity of the gastric contents diluted 1 in 4; in the fifth, the peptic activity of the gastric contents diluted 1 in 16. It did not seem necessary to insert the results of intervening dilutions, although they were usually made.

| Case No. | T. A. | Pure. | $\frac{1}{4}$ | $\frac{1}{16}$ |
|----------|-------|-------|---------------|----------------|
| 173      | 96    | 8.6   | 6.6           | 5.5            |
| 66       | 52    | 0.0   | 5.2           | 2.8            |
| 168      | 43    | 4.1   | 5.5           | 3.2            |
| 188      | 145   | 5.6   | 7.1           | 5.9            |
| 118      | 90    | 7.8   | 7.5           | 4.3            |
| 151      | 150   | 2.2   | 2.2           | 1.1            |
| 134      | 60    | 8.9   | 8.2           | 5.4            |
| 151      | 150   | 8.3   | 7.9           | 5.8            |
| 151      | 150   | 3.7   | 5.4           | 3.7            |
| 134      | 60    | 0.7   | 3.5           | 3.2            |
| 155      | 106   | 7.4   | 7.3           | 5.3            |
| 139      | 58    | 0.0   | ...           | 2.2            |
| 134      | 90    | 0.8   | 4.5           | 4.8            |
| 110      | 136   | 2.4   | ...           | 1.9            |
| 124      | 40    | 3.2   | 2.4           | 1.2            |
| 118      | 72    | 5.2   | 3.1           | 1.7            |
| H. C.    | 90    | 2.2   | 2.5           | 1.6            |
| H. C.    | 67    | 4.9   | 4.0           | 1.9            |
| H. C.    | 38    | 0.5   | ...           | 1.0            |
| 60       | 44    | 2.6   | 1.8           | 1.1            |
| 73       | 110   | 2.4   | ...           | 1.9            |
| 211      | 92    | 3.6   | 4.4           | 2.3            |
| 216      | 71    | 4.4   | 4.1           | 2.8            |

H. C. = hospital cases.

It will be seen that, according to Schuetz's law, the length of the column of albumin digested in the Mett tube should be, in the fourth column, twice that in the fifth, and in the third column, twice that of the fourth, or four times that of the fifth. In 5 cases the number in the fourth column is approximately twice as great as in the fifth, indicating that, in a dilution of 1 to 4, the inhibitory factors had been overcome. In no instance is the third column either twice as great as the fourth, or four times as great as the fifth. The average in the different columns is, for the third, 3.9 mm.; for the fourth, 4.8 mm., and for the fifth, 3.16 mm. In 2 cases the inhibition was complete, although in both digestive activity was present in higher dilutions (cases of *achylia gastrica* in which peptic activity was not manifest in the dilutions have been omitted). This table shows that the statement so frequently made, that in hyperacidity the peptic activity is at least normal, is entirely fallacious. In 1 of the negative cases the total acidity was 52, and in the other 58. In 2 cases, in which only a trace of digestion occurred in the pure gastric juice, the total acidity was 60 and 38. Inhibition was very pronounced in 1 case with a total acidity of 150, and in another with a total acidity of 145, and there was apparently an actual deficit in the peptic activity in the case with a total acidity of 136. These cases resemble in many respects *achylia gastrica*. It is obvious that in such cases the administration of alkalies alone can be of no benefit in restoring gastric digestion, but that the object of treatment should be to remove or diminish the inhibitory factors, because the results of the higher dilutions indicate that latent peptic activity exists in the undiluted gastric contents.

The literature upon the subject of inhibition by food and the products of digestion is not considerable. Nierenstein and Schiff believe that the carbohydrates have an active inhibitory power. Pawlow calls attention to the fact that the administration of oil greatly diminishes the secretion of the gastric juice, but he did not study its effects upon the digestive powers of the juice after secretion.

Pick is the only investigator who appears to have done much work upon this subject. His method differed in details from our own. He used a 2 per cent. solution of Merck's pepsin scales in  $\frac{N}{20}$  HCl. Of this solution 20 c.c. were placed in a Stender dish with the Mett tubes, and the substance to be tested added in bulk. The whole was then placed in an incubator for twenty-four hours. Certain minor objections can be made to this technique. Excepting in a few cases it fails to determine the limits of inhibition. The substances added may alter the chemical reaction of the solution, or may act to a certain extent mechanically. The great advantage of his method is that it enabled him to make a large number of experiments within a comparatively short period of time, and therefore to cover more ground than could possibly have been

done had he made more elaborate studies. He explains inhibition strictly according to the theory of ions. The electronegative ions inhibit peptic activity, and, therefore, those chemical compounds in which they predominate diminish proteolysis.

We used, wherever possible, solutions of known strength of the substances employed, and made a series of dilutions of these solutions, so that by comparing the final results with a series of controls, and repeating the experiments, it was possible to determine the points at which inhibition became manifest, and was absolute.

The effect of proteids was studied in various ways. 10 c.c. of a 5 per cent. solution of egg albumen were added to 5 c.c. of a 2 per cent. solution of pepsin, the object being to determine whether the digestion of egg albumen inhibited the digestion of the Mett tubes. There was no inhibition. A cylinder of egg albumen 1 cm. in diameter was then coagulated by prolonged boiling, and disks 4 mm. in thickness were cut from it and placed in the Stender dishes in place of the albumen solution, it being thought that perhaps there was not enough albumen in the other experiment. No inhibition, however, was observed. A similar experiment was then performed, but the Mett tubes were added only after the albumin had been digested for twelve hours, at the end of which period it was in fact entirely dissolved. Twelve hours later the average digestion was 3.3 mm. and of the control tubes 5.3 mm., indicating active inhibition as a result of the presence of the products of proteid digestion. In order to deal with a measurable solution we used Witte's peptone. The following series show its inhibitory power. In the first table 5 c.c. of a 1 per cent. pepsin solution was employed, and in the second table 5 c.c. of filtered gastric contents with a total acidity of 80.

| Per cent.      | Pepsin. | g. c. | Per cent.      | Pepsin. | g. c. |
|----------------|---------|-------|----------------|---------|-------|
| 10             | 0.0     | 0.0   | $\frac{5}{8}$  | 2.7     | 0.9   |
| 5              | 0.0     | 0.0   | $\frac{5}{16}$ | 3.0     | 0.8   |
| $2\frac{1}{2}$ | 0.2     | 0.4   | Control        | 2.9     | 0.7   |
| $1\frac{1}{4}$ | 2.4     | 0.7   |                |         |       |

g. c. == gastric contents.

This shows that inhibition is absolute if the peptone or albumose present amounts to 5 per cent. by weight of the total, that it is still considerable for 2.5 per cent., but that it practically ceases about 1 per cent. Pick also found that Witte's peptone inhibited gastric digestion. To what extent this inhibitory activity is manifest in the stomach is difficult to determine. The methods for precipitating albumose carry down pepsin also, so that it is impossible to decide whether the removal of the peptone would restore peptic activity or not; and dialysis is too slow to be practicable. It seems difficult to understand how, in the two or three hours that the food remains in the stomach, enough albumose can be formed to produce

a strong degree of inhibition, and there is no evidence to show that the inhibition is greater after a proteid meal than after an ordinary test breakfast of bread and water.

Somewhat akin to proteids is gelatin. We used the white transparent gelatin strips commonly employed in bacteriology. 1 c.c. of a 1 per cent. pepsin solution was employed as the digestant.

| Per cent.      | Pepsin. | g. c. | Per cent.     | Pepsin. | g. c. |
|----------------|---------|-------|---------------|---------|-------|
| 10             | 0.0     | 0.0   | $\frac{1}{4}$ | 2.6     | 1.5   |
| 5              | 0.5     | trace | $\frac{5}{8}$ | 2.5     | 1.7   |
| $2\frac{1}{2}$ | 3.0     | 1.2   | Control       | 2.5     | 1.9   |

Presumably at a point slightly below 10 per cent. inhibition is absolute. It practically disappears at 2.5 per cent.

In testing carbohydrates we used first a solution of cane sugar dissolved in  $\frac{n}{20}$  HCl. The digestant was 5 c.c. of a 2 per cent. solution of pepsin, in one series, and 5 c.c. of filtered gastric contents with a total acidity of 110, in the other series. Only one set of results in each series is given. Other series were practically the same.

| Per cent.      | Pepsin. | g. c. | Per cent.      | Pepsin. | g. c. |
|----------------|---------|-------|----------------|---------|-------|
| 10             | 1.0     | 0.0   | $\frac{5}{8}$  | 2.2     | 2.5   |
| 5              | 1.7     | 2.7   | $\frac{5}{16}$ | 3.1     | ...   |
| $2\frac{1}{2}$ | 2.2     | 2.4   | Control        | 2.8     | 3.0   |
| $1\frac{1}{4}$ | 1.9     | 3.1   |                |         |       |

In the pepsin group the digestive activity of one and one-quarter seems inaccurate. In three other series there was no diminution at this point. Practically, therefore, there is marked inhibition at 10 per cent., slight at 5 per cent., and little or none at 2.5 per cent.

In testing Merck's dextrose we used 5 c.c. of a 1 per cent. pepsin solution and 5 c.c. of filtered gastric contents with a total acidity of 80.

| Per cent.      | Pepsin. | g. c. | Per cent.      | Pepsin. | g. c. |
|----------------|---------|-------|----------------|---------|-------|
| 10             | 2.4     | 1.1   | $\frac{5}{8}$  | 4.3     | 2.0   |
| 5              | 3.2     | 1.6   | $\frac{5}{16}$ | 4.4     | 1.9   |
| $2\frac{1}{2}$ | 3.5     | 1.8   | Control        | 4.1     | 2.1   |
| $1\frac{1}{4}$ | 4.0     | 2.0   |                |         |       |

There was slight inhibitory activity above 2.5 per cent. In testing Merck's maltose 5 c.c. of a 1 per cent. pepsin solution was employed. The following is a typical series:

| Per cent.      |     | Per cent.      |     |
|----------------|-----|----------------|-----|
| 40             | 0.0 | $1\frac{1}{4}$ | 2.5 |
| 10             | 2.4 | $\frac{5}{8}$  | 2.4 |
| 5              | 2.4 | Control        | 2.5 |
| $2\frac{1}{2}$ | 2.6 |                |     |

Maltose, therefore, in dilutions of 10 per cent. or less has no inhibitory activity.

Lactose gave the following result with 1 c.c. of 1 per cent. pepsin solution:

| Per cent.      |     | Per cent. |     |
|----------------|-----|-----------|-----|
| supersaturated | 0.9 | 5         | 1.7 |
| 20             | 1.1 | Control   | 1.8 |

On the whole the inhibitory activity of the carbohydrates is slight and not apparent in solutions of a strength likely to occur in the stomach contents.

The hydrocarbons were difficult to test. The method was that employed by Pick, olive oil being added to various solutions of pepsin and filtered gastric contents. Of course, the oil did not mix with the solution but remained floating on the surface, and, as was to be expected, no inhibition was manifest. As Pick has shown that acacia has a strong inhibitory action it was not feasible to make emulsions.

Alcohol was tested with 5 c.c. of a 1 per cent. pepsin solution. A number of series were made, the results being practically identical. As, however, the percentage limits in the different series were not always the same we have combined them.

| Per cent. |     | Per cent.     |     |
|-----------|-----|---------------|-----|
| 64        | 0.0 | 2             | 4.4 |
| 32        | 0.0 | 1             | 4.6 |
| 16        | 1.5 | $\frac{1}{2}$ | 4.6 |
| 8         | 3.6 | Control       | 4.3 |
| 4         | 4.2 |               |     |

Complete inhibition, therefore, at 32 per cent.; slight at 16 per cent.; and little or no inhibition in mixtures lower than 8 per cent.

*Conclusions of First Section.* The results of the studies of the inhibition by food and the products of its digestion may be briefly summarized.

Albumin produces no inhibition during digestion.

Albumoses have a strong inhibitory effect. Under normal conditions this inhibition probably is not active in the stomach. Under abnormal conditions, particularly in cases of retention, it may be a serious factor.

Gelatin has a distinct inhibitory effect.

Of the sugars, maltose appears to exert the strongest inhibition, and lactose none at all. It is not probable that this inhibition ordinarily plays a very important role in gastric digestion.

Hydrocarbons apparently do not inhibit; at least, when they are added to the gastric contents.

In view of these results it seems reasonable to conclude that some factor other than the food interferes with the gastric digestion. That it cannot be deficient secretion of pepsin, seems clear from the fact that dilution of the gastric contents outside the body gets rid entirely of the inhibitory factor or factors. It is possible either that some factor is present which prevents activation of the pepsinogen or that some substance is lacking which is necessary to

its activation. The question, however, is complicated. It is difficult to devise experiments which give decisive results; nevertheless, it seems capable of solution.

## II.

The second part of our paper is concerned with the effect of various antiseptics employed in the preservation of foodstuffs. The controversy excited by the use of these substances has been exceedingly bitter, and, as is usually the case, experts have testified for both sides. In testing the effect of these preservatives reliance has hitherto been placed chiefly upon the effect produced by feeding foodstuffs treated with them to human beings or even to the lower animals for a considerable period of time. In some cases, very careful studies have also been made of the urine in order to determine whether they irritate the kidneys during elimination. Only a few attempts have been made to study the direct effect of those preservatives upon the digestive processes, and yet this would seem the most obvious thing to do, and the disturbance of digestion a most likely source of injury. Our investigations must not be considered as more than preliminary. We have endeavored merely to show what are the limits of the inhibitory activity of the preservatives when dissolved in artificial gastric juice or gastric contents. Of course, the same errors that apply to the study of inhibition upon the natural products of digestion apply in this case. Nevertheless, if a substance entirely prevents the proteolytic activity of the pepsin under the favorable conditions of an incubator and twenty-four hours' exposure in the Stender dish, it will certainly be effective in the stomach; and substances that in exceedingly moderate dilutions (such as salicylic acid and sulphite of sodium) interfere with digestion in the incubator, will also interfere with digestion in the stomach. It must not be forgotten that the mere inhibition or non-inhibition of peptic activity does not exhaust the capacity for harm of a particular preservative. Nor has the present series of investigations indicated what effect these substances have upon the proteolytic activity of the pancreatic secretion. The materials used have been, wherever possible, chemically pure.

As a preservative common salt is used principally for meats, fish, and butter. In saturated solution in  $\frac{n}{20}$  HCl, using 1 c.c. of 1 per cent. pepsin or 1 c.c. of gastric contents as a digestant, a trace of digestion occurred when a saturated solution was diluted to one-eighth. The following results were obtained with known percentages:

|      |       |         |     |
|------|-------|---------|-----|
| 1:20 | Trace | 1:160   | 1.7 |
| 1:40 | 0.8   | Control | 1.7 |
| 1:80 | 1.0   |         |     |

Formaldehyde is used chiefly as a preservative for milk, or as a constituent in various preservative or embalming fluids. The dilutions were made with formalin, a 40 per cent. solution of formaldehyde, the active agent. Therefore, in order to obtain percentages of formaldehyde employed, the percentage or dilution that we give must be multiplied by 0.4. The following figures were obtained in different series of experiments:

|      |     |       |     |
|------|-----|-------|-----|
| 1:10 | 0.0 | 1:80  | 1.7 |
| 1:20 | 0.0 | 1:160 | 3.0 |
| 1:40 | 0.6 |       |     |

In this series the controls were unsatisfactory, and it merely indicates that absolute inhibition ceases between 1 to 20 and 1 to 40. In the second series the first column is with 5 c.c. of a 1 per cent. pepsin solution, and the second column is with 5 c.c. of filtered gastric contents of a total acidity of 75.

| I.      |     | II.     |     |
|---------|-----|---------|-----|
| 1:100   | 2.0 | 1:100   | 0.9 |
| 1:200   | 2.6 | 1:200   | 1.2 |
| 1:400   | 2.7 | 1:400   | 1.2 |
| 1:800   | 2.9 | 1:800   | 1.3 |
| 1:1600  | 2.8 | 1:1600  | 1.5 |
| Control | 3.2 | Control | 1.5 |

Very doubtful inhibitory action in dilutions more than 1 to 100. In the beginning several series of tests were made in dilution of 1 to 1000 to 1 to 32,000, but no inhibitory effects were observed. We were rather surprised at the high concentration of formalin necessary to cause complete inhibition. These results agree with those of Bliss and Novy, who found that exposure to 4 per cent. formaldehyde did not destroy pepsin, but do not agree with those of Rideal and Fowlerton and Cassel, who found inhibitory activity. Starling believes that the formaldehyde prevents the digestion of fibrin that has been exposed to it, but has little effect upon the pepsin; perhaps an explanation of the different results.

Benzoic acid and benzoate of sodium are employed very extensively, particularly in preserves, pickles, catsup, etc. Benzoic acid dissolves very slightly in the HCl solution. In dilutions of 1 to 100 or higher the inhibition is absolute. In dilutions above 1 to 800 there appears to be no inhibition.

|        |     |         |     |
|--------|-----|---------|-----|
| 1:200  | 0.6 | 1:3200  | 4.0 |
| 1:400  | 1.5 | 1:6400  | 4.0 |
| 1:800  | 3.2 | 1:12800 | 4.1 |
| 1:1600 | 3.8 |         |     |

Sodium benzoate in dilutions of 1 to 100 also causes complete inhibition. The following figures were obtained in a series of high dilutions, the digestant being 1 c.c. of 1 per cent. solution of pepsin.

|         |     |         |     |
|---------|-----|---------|-----|
| 1 : 200 | 1.6 | 1 : 800 | 2.4 |
| 1 : 400 | 2.0 | Control | 2.5 |

Boric acid is also extensively used. In supersaturated solutions it has no effect whatever upon the peptic digestion. This agrees with the results of Chittenden, Liebreich, and others.

Salicylic acid dissolves very slightly in the acid solution. As nearly as we could determine the saturated solution was about 1 to 500. The digestion was 5 c.c. of a 1 per cent. solution of pepsin. The results were as follows:

|          |     |           |     |
|----------|-----|-----------|-----|
| 1 : 750  | 3.5 | 1 : 12000 | 5.0 |
| 1 : 1500 | 3.9 | 1 : 24000 | 6.1 |
| 1 : 3000 | 4.3 | Control   | 7.3 |
| 1 : 6000 | 4.7 |           |     |

With 1 c.c. of a 1 per cent. solution of pepsin the results were as follows:

|           |     |           |     |
|-----------|-----|-----------|-----|
| 1 : 200   | 0.8 | 1 : 20000 | 2.2 |
| 1 : 1000  | 2.0 | 1 : 40000 | 2.3 |
| 1 : 10000 | 2.1 | Control   | 2.3 |

Sodium salicylate, when added to the HCl solution, is precipitated as crystals of salicylic acid, and the effects are probably the same. In all the dilutions which we employed there was total inhibition.

Sulphite of sodium is used in enormous quantities by butchers to restore the red color to the surface of meats that have been exposed to the air. In all dilutions lower than 1 to 100 it produced total inhibition. In the higher dilutions the results were as follows:

|         |     |                   |     |
|---------|-----|-------------------|-----|
| 1 : 200 | 0.7 | 1 : 1600          | 3.4 |
| 1 : 400 | 2.0 | 1 : 3200          | 3.8 |
| 1 : 800 | 2.8 | Control (average) | 4.3 |

Even in dilutions as high as 1:1600, therefore, there is distinct trace of inhibition. It seems that this renders sodium sulphite particularly deleterious for employment upon meats.

Saltpetre (potassium nitrate) is another preservative frequently used. We did not determine the point at which it caused absolute inhibition. Solutions of 1 to 400 still showed slight inhibitory power.

Resorcin is not, as far as we know, used as a preservative, but was tested merely because of its extensive employment as an anti-fermentative and antiseptic in gastric conditions. The digestant was 1 c.c. of 1 per cent. solution of pepsin.

|         |     |         |     |
|---------|-----|---------|-----|
| 1 : 12  | 0.0 | 1 : 200 | 2.1 |
| 1 : 25  | 1.1 | 1 : 400 | 2.0 |
| 1 : 50  | 1.6 | Control | 2.2 |
| 1 : 100 | 1.6 |         |     |

Inhibition ceases, therefore, if the dilution is in excess of 1 to 100.

Guaiacol carbonate is used for the same purpose as resorcin. It is almost completely insoluble in the HCl solution. The results were as follows:

|                             |     |                        |     |
|-----------------------------|-----|------------------------|-----|
| Supersaturated solution     | 2.0 | $\frac{1}{4}$ strength | 2.3 |
| Saturated solution filtered | 2.2 | $\frac{1}{8}$          | 2.3 |
| $\frac{1}{2}$ strength      | 2.2 | Control                | 2.2 |

Therefore, it has practically no inhibitory effect.

Creosote is also used as an antiseptic in gastric conditions and is one of the substances deposited in foods preserved by smoking. Creosote-water is prepared by mixing one part creosote to 100 parts water, agitating and filtering. The amount of creosote that goes into solution appears to be very small. We used  $\frac{n}{20}$  HCl instead of water. The following figures were obtained, the digestant being 1 c.c. of a 1 per cent. pepsin solution:

|               |        |                |     |
|---------------|--------|----------------|-----|
| Pure.         | Trace. | $\frac{1}{8}$  | 1.6 |
| $\frac{1}{2}$ | 0.6    | $\frac{1}{16}$ | 1.9 |
| $\frac{1}{4}$ | 1.0    | Control        | 1.7 |

A few drops of creosote were added to 15 c.c. of the 1 per cent. solution of pepsin. There was a barely recognizable trace of digestion in the tubes.

*Conclusions of Section II.* Of the ordinary preservatives boric acid and borax may be regarded as without effect upon the peptic digestion.

Formaldehyde and alcohol appear to inhibit gastric digestion only when in high concentration.

Salicylic acid has a distinct inhibitory effect even in very high dilutions. This would seem to suggest that its reckless use may cause considerable impairment of nutrition.

Benzoic acid, sodium benzoate, and sodium sulphite inhibit very strongly gastric digestion.

Resorcin inhibits very slightly.

Creosote inhibits strongly, even in the high dilutions in which it is soluble in water or in acid solution.

On the other hand, carbonate of guaiacol, probably on account of its extreme insolubility in acid solutions, appears to have no inhibitory effect whatever.

### III.

In the third section of the paper we report some experiments and investigations which had for their object the discovery of some method of diminishing the inhibitory activity of the gastric contents. It is certain that the inhibitory factor is destroyed by sufficient dilution, and that this dilution does not affect—excepting proportionately—peptic activity. Therefore, attempts were made to

determine the effect of dilution upon the digestive power of the stomach contents. The method employed was that of Mathieu and Rémond for the determination of the total quantity of the gastric contents. After the withdrawal of a test meal 300 c.c. of water were introduced into the stomach and mixed as thoroughly as possible with the remaining stomach contents. It was then withdrawn. By estimating the total acidity of the test meal and of the diluted test meal it was possible to determine just what fraction of the latter consisted of stomach contents; that is to say, supposing the total acidity of the test meal was 100, and of the diluted test meal was 20, the diluted test meal must consist of four parts of water and one part stomach contents. Theoretically, then, if the stomach contents were diluted to such a point that inhibition was overcome (that is 1 in 16), it should possess a digestive power compared with that of the diluted test meal (further diluted 1 to 16) equivalent to the square root of five, or, to state it more generally, equivalent to the square root of the filtered test meal. In a series of these test meals we obtained the following result

| Case.   | T. A. | Pure. | $\frac{1}{4}$ | $\frac{1}{16}$ |
|---------|-------|-------|---------------|----------------|
| H. C.   | 90.0  | 2.2   | 2.5           | 1.6            |
| Diluted | 17.0  | 2.6   | 2.1           | 1.6            |
| 110     | 136.0 | 3.4   | ...           | 1.9            |
| Diluted | 42.0  | 1.4   | 2.5           | 1.1            |
| 124     | 90.0  | 0.8   | 4.8           |                |
| Diluted | 19.0  | 0.6   | 3.4           |                |
| 93      | 112.0 | 3.6   | 4.7           |                |
| Diluted | 7.0   | 0.0   | 2.4           |                |
| 151     | 70.0  | 6.7   | 4.5           |                |
| Diluted | 5.5   | 1.0   | 2.5           |                |
| 134     | 60.0  | 8.9   | 8.2           | 5.4            |
| Diluted | 8.6   | 2.8   | 4.6           | 3.3            |
| 97      | 66.0  | 9.0   | 7.9           | 5.2            |
| Diluted | 2.8   | 0.0   | 3.2           | 1.7            |
| 151     | 150.0 | 8.3   | 7.9           | 5.8            |
| Diluted | 13.5  | 4.1   | 4.4           | 3.0            |

In several cases the total acidity of the diluted portion was too low to permit digestion to proceed, and therefore the results were apparently negative. But in each instance it will be seen that when the acidity was restored by dilution (1 in 16) digestion became active. In no instance was the peptic activity of the diluted test meal (at a dilution of 1 in 16) as low as it should have been by the calculation, and in many instances it was almost as high as that of the test meal itself. There seems to be but two explanations: The introduction of the diluting fluid either stimulated the secretion of the pepsin, or else it converted some inactive form of pepsin into the active substance. In either case it caused a relatively great increase in the digestive power of the stomach contents. The therapeutic indication is not clear, but it would seem that the ingestion of large quantities of fluid in the late stage of digestion—that is

one or two hours after taking a meal—might considerably enhance the digestive activity of the stomach. Of course, it might have, in addition, some injurious effect either upon the motility of the stomach or upon the digestive activity of the intestine. Neither of these points has been determined.

These experiments are interesting from another point of view, that is, from the standpoint of the doctrine of antipepsin. This subject has already been discussed, but these experiments show conclusively, we think, that some factor other than merely concentration is present diminishing the activity of the gastric contents. Otherwise the dilution of the original test meal should, at some stage, give results strictly proportionate to a similar dilution of the diluted test meal, and this appears not to be the case.

If the mere ingestion of a considerable quantity of water can stimulate the production of active pepsin, there may be some method of stimulating the secretion of active pepsin in the gastric juice in cases in which it is ordinarily deficient or absent. In 1888, Jaworski called attention to the fact that in cases of achylia gastrica, if a dilute solution of HCl was introduced into the stomach and allowed to remain for an interval of time, pepsin could be demonstrated in practically all cases. This statement we attempted to verify. As a general thing the method employed was to withdraw the test meal, then to introduce from 200 to 500 c.c. of  $\frac{n}{20}$  HCl, which was allowed to remain from fifteen to thirty minutes. The peptic activity of the test meal and of the HCl solution was then tested. Altogether we have had four cases of achylia gastrica in which repeated examinations had failed to show any trace of peptic activity, either in the pure or diluted stomach contents, and one case of carcinoma of the stomach, confirmed by operation, in which there was a distinct trace of peptic digestion, both in the stomach contents and in the HCl dilution.

| Case.                        |                                                                  | T. A. | Pure. | $\frac{1}{4}$ | $\frac{1}{16}$ |
|------------------------------|------------------------------------------------------------------|-------|-------|---------------|----------------|
| 99                           | . . . . .                                                        | 22    | 0.0   | ...           | 0.0            |
|                              | 200 c.c. $\frac{n}{20}$ HCl fifteen minutes in stomach . . . . . | ...   | 1.3   | 1.3           | 1.9            |
| H. C.                        | . . . . .                                                        | ...   | 0.0   | 0.0           | 0.0            |
|                              | 500 c.c. $\frac{n}{20}$ HCl twenty minutes in stomach . . . . .  | ...   | 1.2   | ...           | 0.5            |
| 54                           | . . . . .                                                        | 20    | 0.0   | 0.0           | 0.0            |
|                              | 300 c.c. $\frac{n}{20}$ HCl fifteen minutes in stomach . . . . . | 50    | 0.0   | 1.5           | ...            |
| H. C. (Carcinoma of stomach) | . . . . .                                                        | ...   | ...   | 0.4           | 0.3            |
|                              | 300 c.c. $\frac{n}{20}$ HCl fifteen minutes in stomach . . . . . | ...   | 3.7   | 2.8           | 1.4            |
| 53                           | . . . . .                                                        | ...   | 0.0   | 0.0           | 0.0            |
|                              | 300 c.c. $\frac{n}{20}$ HCl fifteen minutes in stomach . . . . . | 60    | 2.9   | 3.9           | 1.6            |

Whether the HCl serves merely to activate the pepsinogen, or also as a stimulant to its secretion, it is impossible to say. Presumably

the latter, because in several of these cases the amount of acid present in the gastric contents was sufficient to make digestion possible had there been any proteolytic ferment. The method, unfortunately, does not seem to be of value in distinguishing between carcinoma of the stomach and non-malignant achylia gastrica, although our investigations are still too few to enable us to speak with any certainty on this point. It does yield, however, a very distinct therapeutic indication, that is, that in cases of achylia gastrica the HCl should be administered *before*, and not after, meals. It should also be administered in sufficient strength and bulk to insure active stimulation of the gastric mucous membrane. Of three cases of achylia, all of which have received it in this manner, two have been greatly benefited; the third had been brought in a fairly good condition by several years' treatment before it was employed.

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### ACUTE UNILATERAL SEPTIC PYELONEPHRITIS.

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DURING the past seven or eight years, surgeons have been greatly interested in a class of cases which had been previously regarded as beyond the scope of operative treatment. Up to 1899 one finds a few scattered reports of cases of acute unilateral pyelonephritis of the suppurative type which were operated upon. This condition was known as "surgical kidney" by our medical forefathers, because